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09/813,408	03/21/2001	Simon Delagrave	HER-0041	2931

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EXAMINER	
TRAN, MY CHAU T	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 02/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/813,408	DELAGRAVE ET AL.	
	Examiner	Art Unit	
	MY-CHAU T TRAN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/4/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11-16 and 18-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,11-16 and 18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicant's amendment filed 08/04/2004 is acknowledged and entered. Claims 2 and 17 have been canceled. Claims 1 and 11 have been amended.

2. Claim 22 was canceled; and Claim 16 was amended by the amendment filed on 1/20/2004.

3. Claims 10, and 23-56 were canceled and Claim 11 was amended by the amendment filed on 6/26/2003. Additionally in view of the amendment to claim 11, Claims 11-21 are rejoined with the elected invention of claims 1-9.

4. Claims 1, 3-9, 11-16, and 18-21 are pending.

5. Claims 1, 3-9, 11-16, and 18-21 are treated on the merit in this Office Action.

Withdrawn Rejections

6. The rejection of claims 1-2, 4-9, 11-15, 17, and 19-21 under 35 USC 103(a) as being obvious over Hunkapiller et al. (US Patent 5,942,609) has been withdrawn and applicant's arguments are considered but are moot in view of the new grounds of rejection.

7. The rejection of claims 1-9, 11-15, and 17-21 under 35 USC 103(a) as being obvious over Hunkapiller et al. (US Patent 5,942,609) and Walker et al. (*PNAS*, **1975**, 72(1):122-126) has been withdrawn and applicant's arguments are considered but are moot in view of the new grounds of rejection.

8. The rejection of claims 1-4, 6-9, 11-13, and 17-21 under 35 USC 103(a) as being obvious over Hyman (US Patent 5,602,000) has been withdrawn and applicant's arguments are considered but are moot in view of the new grounds of rejection.

9. The rejection of claims 1-4, 6-9, 11-13, and 16-21 under 35 USC 103(a) as being obvious over Hyman (US Patent 5,602,000) and Langer et al. (*PNAS*, **1981**, 78(1):6633-6637) has been withdrawn and applicant's arguments are considered but are moot in view of the new grounds of rejection.

10. The judicially created doctrine of obviousness-type double patenting rejection of claims 1-5, 7-8, 11-15 and 17-18 over claims 1, 7, 10, 12, 14, 18, 20-21, and 24-26 of U.S. Patent No. 6,479,262 B1 has been withdrawn and applicant's arguments are considered but are moot in view of the new grounds of rejection.

11. The judicially created doctrine of obviousness-type double patenting rejection of claims 1-9, and 11-21 over claims 1-4, 7-9, 11-14, and 17-22 of U.S. Patent No. 6,635,453 B2 has been

withdrawn and applicant's arguments are considered but are moot in view of the new grounds of rejection.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 3, 6-8, 11-13, 18, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (*Nucleic Acids Research*, **1996**, 24(5), pgs. 990-991).

The instant invention recites a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides. The method comprises the steps of (a) coupling the oligonucleotides by ligating with a ligase or ribozyme to form a plurality of coupled oligonucleotides, and (b) assembling the polynucleotide by extension of the coupled oligonucleotide. Each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide.

Zhang et al. disclose a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides (see e.g. pg. 990, left col., lines 11-24; pg. 990, right col., lines 22-36; pg. 991, fig. 1). The method comprises the steps of 1) a gene-specific primer is extended by PCR to produce single-stranded DNA extension products; 2) the single-stranded DNA extension products is ligated to an arbitrary oligonucleotide with T4 RNA ligase to create templates (refers to the presently claimed step (a) of claim 1; claims 3, 8, and 18); 3) the templates are amplified by PCR and followed by a final extension (refers to the presently claimed step (b) of claim 1; claims 6 and 20) to produce polynucleotide having a target sequence

(refers to the present claim 12) (see e.g. pg. 990, left col., lines 11-24; pg. 990, left col., line 25 thru right col., line 21; pg. 991, fig. 1). Additionally, Zhang et al. in the ligating step, i.e. the single-stranded DNA extension products ligation mediated by T4 RNA ligase, the 3'-hydroxyl group of the 5'-P-donor oligo, i.e. arbitrary oligonucleotide, is block in order to increase the efficiency of the ligating DNA molecule with T4 RNA ligase (refers to the present claims 7, and 11) (see e.g. pg. 991, left col., lines 3-5). The gene-specific primer and arbitrary oligonucleotide comprises 20 mer oligonucleotides (refers to the present claim 13) (see e.g. pg. 990, left col., line 25 thru right col., line 21; pg. 991). The arbitrary oligonucleotide is 5'-AGGGTGCCAACCTCTTCAAG-3' (refers to the presently claimed limitation of wherein each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide) (see e.g. pg. 990, left col., line 25 thru right col., line 21; pg. 991). Therefore the method of Zhang et al. anticipates the presently claimed method.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1, 3, and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (*Nucleic Acids Research*, **1996**, 24(5), pgs. 990-991) and Ho et al. (*Gene*, **1989**, 77(1), pgs. 51-59).

The instant invention recites a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides. The method comprises the steps of (a) coupling the oligonucleotides by ligating with a ligase or ribozyme to form a plurality of coupled oligonucleotides, and (b) assembling the polynucleotide by extension of the coupled oligonucleotide. Each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide.

Zhang et al. disclose a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides (see e.g. pg. 990, left col., lines 11-24; pg. 990, right col., lines 22-36; pg. 991, fig. 1). The method comprises the steps of 1) a gene-specific primer is extended by PCR to produce single-stranded DNA extension products; 2) the single-stranded DNA extension products is ligated to an arbitrary oligonucleotide with T4 RNA ligase to create templates (refers to the presently claimed step (a) of claim 1; claims 3, and 8); 3) the templates are amplified by PCR and followed by a final extension (refers to the presently claimed step (b) of claim 1; claim 6) to produce polynucleotide having a target sequence (see e.g. pg. 990, left col., lines 11-24; pg. 990, left col., line 25 thru right col., line 21; pg. 991, fig. 1). Additionally, Zhang et al. in the ligating step, i.e. the single-stranded DNA extension products ligation

mediated by T4 RNA ligase, the blocking 3'-hydroxyl group of the 5'-P-donor oligo, i.e. arbitrary oligonucleotide, is block in order to increase the efficiency of the ligating DNA molecule with T4 RNA ligase (refers to the present claim 7) (see e.g. pg. 991, left col., lines 3-5). The gene-specific primer and arbitrary oligonucleotide comprises 20 mer oligonucleotides (see e.g. pg. 990, left col., line 25 thru right col., line 21; pg. 991). The arbitrary oligonucleotide is 5'-AGGGTGCCAACCTCTTCAAG-3' (refers to the presently claimed limitation of wherein each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide) (see e.g. pg. 990, left col., line 25 thru right col., line 21; pg. 991).

The method of Zhang et al. differs from the presently claimed invention by failing to modify the extension step by using overlap PCR.

Ho et al. disclose the method of overlap extension using PCR (see e.g. Abstract; pg. 52, left col., lines 31-49; pg. 53, left col., line 36 thru right col., line 7; pg. 53, right col., lines 23-48; pg. 54, figs. 1 and 2). The method comprises joining two DNA fragments having overlapping ends forming the 'fusion' product, i.e. overlap extension of the DNA fragments, and amplified by PCR (see e.g. pg. 53, right col., lines 23-48; pg. 54, figs. 1 and 2). One advantage of this method is providing a flexible method of site-directed mutagenesis wherein the variety of sequence alterations can be achieved (see e.g. pg. 54, lines 1-4).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the extension step by using overlap PCR as taught by Ho et al. in the method of Zhang et al. One of ordinary skill in the art would have been motivated to modify the extension step by using overlap PCR in the method of Zhang et al. for the advantage of

providing a flexible method of site-directed mutagenesis wherein the variety of sequence alterations can be achieved (Ho: pg. 54, lines 1-4) since both Zhang et al. and Ho et al. disclose the method of extension by PCR (Zhang: pg. 990, left col., lines 11-24; Ho: pg. 52, left col., lines 31-49). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Zhang et al. and Ho et al. because Ho et al. disclose the success of the overlap extension using PCR by way of examples (see e.g. pg. 55, fig. 3, and pg.56, fig. 4).

17. Claims 1, 11-13, 16, 18, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (*Nucleic Acids Research*, **1996**, 24(5), pgs. 990-991).

The instant invention recites a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides. The method comprises the steps of (a) coupling the oligonucleotides by ligating with a ligase or ribozyme to form a plurality of coupled oligonucleotides, and (b) assembling the polynucleotide by extension of the coupled oligonucleotide. Each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide.

Zhang et al. disclose a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides (see e.g. pg. 990, left col., lines 11-24; pg. 990, right col., lines 22-36; pg. 991, fig. 1). The method comprises the steps of 1) a gene-specific primer is extended by PCR to produce single-stranded DNA extension products; 2) the single-stranded DNA extension products is ligated to an arbitrary oligonucleotide with T4 RNA ligase to create templates (refers to the presently claimed step (a) of claim 1; claim 18); 3) the templates are amplified by PCR and followed by a final extension (refers to the presently claimed step (b) of claim 1; claim 20) to produce polynucleotide having a target sequence (refers to the present claim 12) (see e.g. pg. 990, left col., lines 11-24; pg. 990, left col., line 25 thru right col., line 21;

pg. 991, fig. 1). Additionally, Zhang et al. in the ligating step, i.e. the single-stranded DNA extension products ligation mediated by T4 RNA ligase, the blocking 3'-hydroxyl group of the 5'-P-donor oligo, i.e. arbitrary oligonucleotide, is block in order to increase the efficiency of the ligating DNA molecule with T4 RNA ligase (refers to the present claim 11) (see e.g. pg. 991, left col., lines 3-5). The gene-specific primer and arbitrary oligonucleotide comprises 20 mer oligonucleotides (refers to the present claim 13) (see e.g. pg. 990, left col., line 25 thru right col., line 21; pg. 991). The arbitrary oligonucleotide is 5'-AGGGTGCCAACCTCTTCAAG-3' (refers to the presently claimed limitation of wherein each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide) (see e.g. pg. 990, left col., line 25 thru right col., line 21; pg. 991).

The method of Zhang et al. differs from the presently claimed invention by failing to include in the blocking step using biotin-dideoxyuridine triphosphate blocking group.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include in the blocking step using biotin-dideoxyuridine triphosphate blocking group in the method of Zhang et al. One of ordinary skill in the art would have been motivated to include in the blocking step using biotin-dideoxyuridine triphosphate blocking group in the method of Zhang et al. because the type of blocking group use in the blocking step for the method of Zhang et al. would be a choice of experimental design since Zhang et al. disclose that the efficiency of ligating DNA molecules with T4 RNA ligase can be increase by blocking 3'-hydroxyl group of the 5'-P-donor oligo (Zhang: pg. 991, left col., lines 3-5). Thus the type of blocking group use would be a choice of experimental design and is considered

within the purview of the cited prior art. Furthermore, one of ordinary skill in the art would have reasonably expectation of success in using biotin-dideoxyuridine triphosphate blocking group in the blocking step for the method of Zhang et al. because the taught method would need no modification other than the type of blocking group use that do not materially affect the method steps.

18. Claims 1, 11-13, and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (*Nucleic Acids Research*, **1996**, 24(5), pgs. 990-991) and Hinton et al. (*Nucleic Acid Research*, **1982**, 10(6), pgs. 1877-1894).

The instant invention recites a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides. The method comprises the steps of (a) coupling the oligonucleotides by ligating with a ligase or ribozyme to form a plurality of coupled oligonucleotides, and (b) assembling the polynucleotide by extension of the coupled oligonucleotide. Each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide.

Zhang et al. disclose a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides (see e.g. pg. 990, left col., lines 11-24; pg. 990, right col., lines 22-36; pg. 991, fig. 1). The method comprises the steps of 1) a gene-specific primer is extended by PCR to produce single-stranded DNA extension products; 2) the single-stranded DNA extension products is ligated to an arbitrary oligonucleotide with T4 RNA ligase to create templates (refers to the presently claimed step (a) of claim 1; claim 18); 3) the templates are amplified by PCR and followed by a final extension (refers to the presently claimed step (b) of claim 1; claim 20) to produce polynucleotide having a target sequence (refers to the present claim 12) (see e.g. pg. 990, left col., lines 11-24; pg. 990, left col., line 25 thru right col., line 21;

pg. 991, fig. 1). Additionally, Zhang et al. in the ligating step, i.e. the single-stranded DNA extension products ligation mediated by T4 RNA ligase, the blocking 3'-hydroxyl group of the 5'-P-donor oligo, i.e. arbitrary oligonucleotide, is block in order to increase the efficiency of the ligating DNA molecule with T4 RNA ligase (refers to the present claim 11) (see e.g. pg. 991, left col., lines 3-5). The ligation step includes the cosubstrate of ATP (see e.g. pg. 990, left col., line 40 to right col., line 1). The gene-specific primer and arbitrary oligonucleotide comprises 20 mer oligonucleotides (refers to the present claim 13) (see e.g. pg. 990, left col., line 25 thru right col., line 21; pg. 991). The arbitrary oligonucleotide is 5'-AGGGTGCCAACCTCTTCAAG-3' (refers to the presently claimed limitation of wherein each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide) (see e.g. pg. 990, left col., line 25 thru right col., line 21; pg. 991).

The method of Zhang et al. differs from the presently claimed invention by failing to include the wash step, i.e. the step of washing the activated oligonucleotide to form washed oligonucleotide.

Hinton et al. disclose the synthesis of define sequences of oligodeoxyribonucleotides using T4 RNA ligase (see e.g. Abstract; pg. 1879, line 8 thru pg. 1880, line 3; pg. 1883, line 3 thru pg. 1885, line 8; pg. 1884, Table 3, and fig. 3). The method comprises reacting two oligomers with T4 RNA ligase, and ATP, and purifying the reaction product (see e.g. pg. 1879, line 8 thru pg. 1880, line 3; pg. 1884, lines 3-5). The purification step removes the unreacted substrates and is performed by chromatography on paper in solvent.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include the wash step, i.e. the step of washing the activated oligonucleotide to form washed oligonucleotide as taught by Hinton et al. in the method of Zhang et al. One of ordinary skill in the art would have been motivated to include the wash step, i.e. the step of washing the activated oligonucleotide to form washed oligonucleotide in the method of Zhang et al. for the advantage of removing unreacted substrates (Hinton: lines 3-5) since both Zhang et al. and Hinton et al. disclose the method of coupling oligonucleotides via T4 RNA ligase and use the cosubstrate of ATP (Zhang: pg. 990, left col., lines 17-21; fig. 1; Hinton: Abstract; pg. 1879, line 7 thru pg. 1880, line 3; pg. 1884, Table 3). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Zhang et al. and Hinton et al. because Hinton et al. disclose the success of removing unreacted substrates (Hinton: pg. 1884, fig. 3).

19. Claims 1, 11-13, 18, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (*Nucleic Acids Research*, **1996**, 24(5), pgs. 990-991) and Ho et al. (*Gene*, **1989**, 77(1), pgs. 51-59).

The instant invention recites a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides. The method comprises the steps of (a) coupling the oligonucleotides by ligating with a ligase or ribozyme to form a plurality of coupled oligonucleotides, and (b) assembling the polynucleotide by extension of the coupled oligonucleotide. Each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide.

Zhang et al. disclose a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides (see e.g. pg. 990, left col., lines 11-24; pg. 990, right col.,

lines 22-36; pg. 991, fig. 1). The method comprises the steps of 1) a gene-specific primer is extended by PCR to produce single-stranded DNA extension products; 2) the single-stranded DNA extension products is ligated to an arbitrary oligonucleotide with T4 RNA ligase to create templates (refers to the presently claimed step (a) of claim 1; claim 18); 3) the templates are amplified by PCR and followed by a final extension (refers to the presently claimed step (b) of claim 1; claim 20) to produce polynucleotide having a target sequence (refers to the present claim 12) (see e.g. pg. 990, left col., lines 11-24; pg. 990, left col., line 25 thru right col., line 21; pg. 991, fig. 1). Additionally, Zhang et al. in the ligating step, i.e. the single-stranded DNA extension products ligation mediated by T4 RNA ligase, the blocking 3'-hydroxyl group of the 5'-P-donor oligo, i.e. arbitrary oligonucleotide, is block in order to increase the efficiency of the ligating DNA molecule with T4 RNA ligase (refers to the present claim 11) (see e.g. pg. 991, left col., lines 3-5). The gene-specific primer and arbitrary oligonucleotide comprises 20 mer oligonucleotides (refers to the present claim 13) (see e.g. pg. 990, left col., line 25 thru right col., line 21; pg. 991). The arbitrary oligonucleotide is 5'-AGGGTGCCAACCTCTTCAAG-3' (refers to the presently claimed limitation of wherein each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide) (see e.g. pg. 990, left col., line 25 thru right col., line 21; pg. 991).

The method of Zhang et al. differs from the presently claimed invention by failing to modify the extension step by using overlap PCR.

Ho et al. disclose the method of overlap extension using PCR (see e.g. Abstract; pg. 52, left col., lines 31-49; pg. 53, left col., line 36 thru right col., line 7; pg. 53, right col., lines 23-48;

pg. 54, figs. 1 and 2). The method comprises joining two DNA fragments having overlapping ends forming the 'fusion' product, i.e. overlap extension of the DNA fragments, and amplified by PCR (see e.g. pg. 53, right col., lines 23-48; pg. 54, figs. 1 and 2). One advantage of this method is providing a flexible method of site-directed mutagenesis wherein the variety of sequence alterations can be achieved (see e.g. pg. 54, lines 1-4).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the extension step by using overlap PCR as taught by Ho et al. in the method of Zhang et al. One of ordinary skill in the art would have been motivated to modify the extension step by using overlap PCR in the method of Zhang et al. for the advantage of providing a flexible method of site-directed mutagenesis wherein the variety of sequence alterations can be achieved (Ho: pg. 54, lines 1-4) since both Zhang et al. and Ho et al. disclose the method of extension by PCR (Zhang: pg. 990, left col., lines 11-24; Ho: pg. 52, left col., lines 31-49). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Zhang et al. and Ho et al. because Ho et al. disclose the success of the overlap extension using PCR by way of examples (see e.g. pg. 55, fig. 3, and pg.56, fig. 4).

20. Claims 1, 3-5, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dehlinger (US Patent 5,723,320) and Hinton et al. (*Nucleic Acid Research*, **1982**, 10(6), pgs. 1877-1894).

The instant invention recites a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides. The method comprises the steps of (a) coupling the oligonucleotides by ligating with a ligase or ribozyme to form a plurality of coupled oligonucleotides, and (b) assembling the polynucleotide by extension of the coupled oligonucleotide. Each of the coupled oligonucleotides represents a region of sequence of

polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide.

Dehlinger discloses the method of producing an array (see Abstract; col. 2, line 49 thru col. 3, line 4; col. 11, line 3 to col. 12, line 56; figs. 10-13). The method comprises 1) synthesizing the oligonucleotide probes on a solid support (refers to presently claims 4, and 7) (see e.g. col. 5, lines 63-67; col. 10, lines 56-67; fig. 10); 2) hybridizing the oligonucleotide probes on a solid support with a set of gene-probe templates (see e.g. col. 2, lines 58-67; col. 11, lines 16-19; col. 12, lines 4-15; figs. 12 and 13); and 3) the oligonucleotides probes on a solid support are the extended by strand-directed polymerization (refers to the presently claimed step (b) of claim 1; claims 5, and 8) (see e.g. col. 3, lines 1-4; col. 11, lines 16-19; figs. 12 and 13). On one side of the solid support the oligonucleotides probes comprises the same six nucleotides, i.e. 5'-ACCGGC-3' (refers to the presently claimed limitation of wherein each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide) (see e.g. col. 11, lines 27-37; fig. 10).

The method of Dehlinger differs from the presently claimed invention by failing to modify the coupling step by using T4 RNA ligase.

Hinton et al. disclose the synthesis of define sequences of oligodeoxyribonucleotides using T4 RNA ligase (see e.g. Abstract; pg. 1879, line 8 thru pg. 1880, line 3; pg. 1883, line 3 thru pg. 1885, line 8; pg. 1884, Table 3, and fig. 3). The method comprises reacting two oligomers with T4 RNA ligase, and ATP, and purifying the reaction product (see e.g. pg. 1879, line 8 thru pg. 1880, line 3; pg. 1884, lines 3-5). The purification step removes the unreacted substrates and is performed by chromatography on paper in solvent.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the coupling step in the method of Dehlinger by using T4 RNA ligase as taught by Hinton et al. One of ordinary skill in the art would have been motivated to modify the coupling step in the method of Dehlinger by using T4 RNA ligase for the advantage of providing a method of joining two oligomers without requiring the use of template strand to align the ends of the two oligomers to be join and RNA ligase can extend deoxyoligomers in either the 5'→ 3' or the 3'→ 5' direction (Hinton: pg. 1891, lines 25-27). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Dehlinger and Hinton et al. because Hinton et al. disclose the success of using T4 RNA ligase to join oligomers (see e.g. pg. 1884, Table 3, and fig. 3; pg. 1887, fig. 5).

21. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dehlinger (US Patent 5,723,320) and Hinton et al. (*Nucleic Acid Research*, **1982**, 10(6), pgs. 1877-1894) as applied to claims 1, 3-5, 7, and 8 above, and further in view of Ho et al. (*Gene*, **1989**, 77(1), pgs. 51-59).

The instant invention recites a method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides. The method comprises the steps of (a) coupling the oligonucleotides by ligating with a ligase or ribozyme to form a plurality of coupled oligonucleotides, and (b) assembling the polynucleotide by extension of the coupled oligonucleotide. Each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide.

The method combination of Dehlinger and Hinton et al. disclose the method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides wherein the oligonucleotides are joined via T4 RNA ligase.

Dehlinger discloses the method of producing an array (see Abstract; col. 2, line 49 thru col. 3, line 4; col. 11, line 3 to col. 12, line 56; figs. 10-13). The method comprises 1) synthesizing the oligonucleotide probes on a solid support (refers to presently claim 4) (see e.g. col. 5, lines 63-67; col. 10, lines 56-67; fig. 10); 2) hybridizing the oligonucleotide probes on a solid support with a set of gene-probe templates (see e.g. col. 2, lines 58-67; col. 11, lines 16-19; col. 12, lines 4-15; figs. 12 and 13); and 3) the oligonucleotides probes on a solid support are the extended by strand-directed polymerization (refers to the presently claimed step (b) of claim 1) (see e.g. col. 3, lines 1-4; col. 11, lines 16-19; figs. 12 and 13). On one side of the solid support the oligonucleotides probes comprises the same six nucleotides, i.e. 5'-ACCGGC-3' (refers to the presently claimed limitation of wherein each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide) (see e.g. col. 11, lines 27-37; fig. 10).

Hinton et al. disclose the synthesis of define sequences of oligodeoxyribonucleotides using T4 RNA ligase (see e.g. Abstract; pg. 1879, line 8 thru pg. 1880, line 3; pg. 1883, line 3 thru pg. 1885, line 8; pg. 1884, Table 3, and fig. 3). The method comprises reacting two oligomers with T4 RNA ligase, and ATP, and purifying the reaction product (see e.g. pg. 1879, line 8 thru pg. 1880, line 3; pg. 1884, lines 3-5). The purification step removes the unreacted substrates and is performed by chromatography on paper in solvent.

Thus it is obvious to combine the method of Dehlinger and Hinton et al. to produce the presently claimed method of preparing a polynucleotide having a target sequence from a plurality of oligonucleotides wherein the oligonucleotides are joined via T4 RNA ligase. Because modifying the coupling step in the method of Dehlinger by using T4 RNA ligase for the

advantage of providing a method of joining two oligomers without requiring the use of template strand to align the ends of the two oligomers to be join and RNA ligase can extend deoxyoligomers in either the 5'→ 3' or the 3'→ 5' direction (Hinton: pg. 1891, lines 25-27).

The method combination of Dehlinger and Hinton et al. differs from the presently claimed invention by failing to modify the extension step by using overlap PCR.

Ho et al. disclose the method of overlap extension using PCR (see e.g. Abstract; pg. 52, left col., lines 31-49; pg. 53, left col., line 36 thru right col., line 7; pg. 53, right col., lines 23-48; pg. 54, figs. 1 and 2). The method comprises joining two DNA fragments having overlapping ends forming the 'fusion' product, i.e. overlap extension of the DNA fragments, and amplified by PCR (see e.g. pg. 53, right col., lines 23-48; pg. 54, figs. 1 and 2). One advantage of this method is providing a flexible method of site-directed mutagenesis wherein the variety of sequence alterations can be achieved (see e.g. pg. 54, lines 1-4).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the extension step by using overlap PCR as taught by Ho et al. in the method combination of Dehlinger and Hinton et al. One of ordinary skill in the art would have been motivated to modify the extension step by using overlap PCR in the method combination of Dehlinger and Hinton et al. for the advantage of providing a flexible method of site-directed mutagenesis wherein the variety of sequence alterations can be achieved (Ho: pg. 54, lines 1-4). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Dehlinger, Hinton et al., and Ho et al. because Ho et al. disclose the success of the overlap extension using PCR by way of examples (see e.g. pg. 55, fig. 3, and pg.56, fig. 4).

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 1, 3-5, 7-8, 11-15, and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, and 12 of U.S. Patent No. 6,479,262 B1 (refers to as Delgrave). Although the conflicting claims are not identical, they are not patentably distinct from each other because the examined claims would have been obvious over the Delgrave claims.

Claim 1 of Delgrave recites a method of preparing a polynucleotides having at least 200 nucleotides and a predetermine nucleotide sequence (refers to the instant claims 1, 12 and 13). The method comprises the steps of 1) providing a solid support; 2) providing a plurality of oligonucleotides, wherein the combination of the nucleotide sequences of said oligonucleotides comprises the nucleotide sequence of said polynucleotide; 3) contacting said solid support with the 3' terminus of a first oligonucleotide from said plurality of oligonucleotides to form a tethered oligonucleotide (refers to instant claims 4, 7, 14, and the instant blocking step of claim 11); 4) ligating the 3' terminus of another oligonucleotide from said plurality of oligonucleotides to the 5' terminus of said tethered oligonucleotide, wherein said ligating is carried out in the

presence of RNA ligase or ribozyme (refers to instant step (a) of claim 1, instant claim 8, and the instant ligating step of claim 11); 5) phosphorylating the 5' terminus of said another oligonucleotide; and 6) repeating steps d) and e) until said polynucleotide is prepared (refers to instant step (b) of claim 1, and instant claim 5). Claim 2 of Delgrave recites the type of solid support (refers to the instant claim 15). Claim 12 of Delgrave recites that RNA ligase is T4 RNA ligase (refers to the instant claims 3, and 18).

The claimed method of Delgrave differs from the instant claim 1 by not including the limitation that each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide. However, figure 2 of Delgrave define that the tethered oligonucleotides, i.e. the oligo attached to a solid support, are either identical copies or each one different. Therefore, it would be obvious that the claimed ligated oligonucleotides in claim 1 step 4 of Delgrave, which include the tethered oligonucleotide, would have include a share terminal region of sequence and the polynucleotide produce by the method in claim 1 of Delgrave would encompasses the instant claim 1 limitation that each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide.

Thus the examined claims 1, 3-5, 7-8, 11-15, and 18 are obvious over the Delgrave claims 1, 2, and 12.

24. Claims 1, 3-9, 11-16, and 18-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-9 of U.S. Patent No. 6,635,453 B2 (refers to as Delgrave et al.) and Ho et al. (*Gene*, **1989**, 77(1), pgs. 51-59).

Claim 1 of Delgrave et al. recites a method of preparing a polynucleotide from a plurality of oligonucleotides (refers to instant claims 1, and 12). The method comprises the steps of a) blocking the 3' terminus of a first oligonucleotide with a blocking group to form a blocked oligonucleotide, wherein said first oligonucleotide comprises the 3' terminus of said polynucleotide (refers to instant claim 7, and the instant blocking step of claim 11); b) coupling the 3' terminus of a further oligonucleotide from said plurality of oligonucleotides to the 5' terminus of said blocked oligonucleotide to form a coupled oligonucleotide; wherein said coupling is carried out in the presence of an RNA ligase or a ribozyme (refers to the instant step (a) of claim 1, instant claim 8, and the instant ligating step of claim 11); c) phosphorylating the 5' terminus of said further oligonucleotide; d) amplifying said coupled oligonucleotide to form an amplified oligonucleotide substantially free of blocking group (refers to instant claims 6, and 20); and e) repeating steps a) to d) with said amplified oligonucleotide until said polynucleotide is prepared (refers to instant step (b) of claim 1). Claims 3, 4 and 6 of Delgrave et al. recite that RNA ligase is T4 RNA ligase (refers to instant claims 3 and 18). Claim 5 of Delgrave et al. recites that the coupling step in claim 1 of Delgrave et al. comprises the steps of contacting said blocked oligonucleotide with RNA ligase and cosubstrate to form activated oligonucleotide, washing said activated oligonucleotide to form washed oligonucleotide, and contacting said washed oligonucleotide with said further oligonucleotide and RNA ligase (refers to instant claim 19). Claim 7 of Delgrave et al. recites that the blocking group is ddUTP-biotin (refers to instant

claim 16). Claims 8 of Delgrave et al. recites that the blocking group is a solid support (refers to instant claims 4, 5, and 14). Claim 9 of Delgrave et al. recites the type of solid support (refers to the instant claim 15).

The claimed method of Delgrave et al. differs from the instant claim 1 by not including the limitation that each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide. However, figure 2 of Delgrave et al. define that the tethered oligonucleotides, i.e. the oligo attached to a solid support, are either identical copies or each one different. Therefore, it would be obvious that the claimed ligated oligonucleotides in claim 1 step 4 of Delgrave et al., which include the tethered oligonucleotide, would have include a share terminal region of sequence and the polynucleotide produce by the method in claim 1 of Delgrave et al. would encompasses the instant claim 1 limitation that each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide.

The claimed method of Delgrave et al. differs from the instant claim 13 by failing to include that the oligonucleotide comprises from about 10 to about 200 nucleotides. However, the specification of Delgrave et al. define the term "oligonucleotide" as having up to about 200 nucleotides (see col. 6, lines 36-41). Thus, it would be obvious that claimed oligonucleotide in claim 1 of Delgrave et al. would encompasses the instant claim 13, i.e. the oligonucleotide having up to about 200 nucleotides.

The claimed method of Delgrave et al. differs from the instant claim 1 by failing to modify the extension step by using overlap PCR (refers to instant claims 9, and 21).

Ho et al. disclose the method of overlap extension using PCR (see e.g. Abstract; pg. 52, left col., lines 31-49; pg. 53, left col., line 36 thru right col., line 7; pg. 53, right col., lines 23-48; pg. 54, figs. 1 and 2). The method comprises joining two DNA fragments having overlapping ends forming the 'fusion' product, i.e. overlap extension of the DNA fragments, and amplified by PCR (see e.g. pg. 53, right col., lines 23-48; pg. 54, figs. 1 and 2). One advantage of this method is providing a flexible method of site-directed mutagenesis wherein the variety of sequence alterations can be achieved (see e.g. pg. 54, lines 1-4).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the extension step by using overlap PCR as taught by Ho et al. in the method of Delgrave et al. One of ordinary skill in the art would have been motivated to modify the extension step by using overlap PCR in the method of Delgrave et al. for the advantage of providing a flexible method of site-directed mutagenesis wherein the variety of sequence alterations can be achieved (Ho: pg. 54, lines 1-4). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Delgrave et al. and Ho et al. because Ho et al. disclose the success of the overlap extension using PCR by way of examples (see e.g. pg. 55, fig. 3, and pg.56, fig. 4).

Thus the examined claims 1, 3-9, 11-16, and 18-21 are obvious over the Delgrave et al. claims 1, 3-9 and Ho et al.

Response to Arguments

25. Applicant's arguments with respect to claims 1, 3-9, 11-16, and 18-21 have been considered but are moot in view of the new grounds of rejection.

26. The obviousness-type double patenting rejections were rewritten to applicant arguments of highsight reasoning regarding the limitation that each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide.

27. This Office Action is made Non-Final to address the limitations of 1) each of the coupled oligonucleotides represents a region of sequence of polynucleotide and shares at least one terminal region of sequence with at least one other coupled oligonucleotide, and 2) extension is carried out using overlap PCR; and also to include new rejections based on newly found art such as Dehlinger (US Patent 5,723,320) and Hinton et al. (*Nucleic Acid Research*, **1982**, 10(6), pgs. 1877-1894).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 571-272-0810. The examiner can normally be reached on Monday: 8:00-2:30; Tuesday-Thursday: 7:30-5:00; Friday: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

mct
February 2, 2005

PADMASHRI PONNALURI
PRIMARY EXAMINER